DRUG DELIVERY—PARENTERAL ROUTE

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INTRODUCTION

The *United States Pharmacopoeia 24* (1) defines a small-volume injectable (SVI) as "an injection that is packaged in containers labeled as containing 100 ml or less." Therefore, all sterile products packaged in vials, ampuls, syringes, cartridges, bottles, or any other container that is 100 ml or less fall under this classification. Ophthalmic products packaged in squeezable plastic containers, although topically applied to the eye rather than administered by injection, also fall under the classification of small-volume injections as long as the container size is 100 ml or less. (See the article Ocular Drug Formulation and Delivery in this encyclopedia). Large-volume injectables (LVI) have to be terminally sterilized, whereas SVIs can be sterilized terminally or by aseptic filtration and processing. In fact, 80% or greater of all SVIs commercially available are prepared by aseptic processing. LVIs usually involve intravenous infusion, dialysis, or irrigation fluids containing electrolytes, sugar, amino acids, blood, blood products, and fatty lipid emulsions (2). LVIs must be administered by intravenous administration. Small-volume injections may be injected by intravenous, subcutaneous, or intramuscular routes (primary routes of parenteral administration) or by various secondary routes such as intra-abdominal, intra-arterial, intra-articular, intracardiac, intracisternal, intradermal, intraocular, intrapleural, intrathecal, intrauterine, or intraventricular injections.

SVI formulations are relatively simple, composed of the active ingredient, a solvent system (preferably aqueous), a minimal number of excipients present for reasons described later in this chapter, and the appropriate container and closure packaging system. If the active ingredient is unstable in solution or suspension, the product can be a dry powder, processed either by lyophilization or by sterile crystallization.

This chapter introduces the basic aspects of small-volume injectable products—their use, types and primary characteristics of dosage forms, formulation ingredients, and packaging systems. Additional information is available in a variety of reference texts and book chapters (2–7). Only conventional SVI formulations are addressed in this chapter. Advanced, long-acting (depot) formulations are not covered.

PRIMARY USES OF SMALL-VOLUME INJECTABLES

Small-volume injectables can be therapeutic injections, ophthalmics, diagnostics, radiopharmaceuticals, or allergenic extracts. The active ingredients can be intended for human or animal therapy and can be small molecules, proteins and other large molecules, biologics, vaccines, monoclonal antibodies, antisense oligonucleotides, and, in the future, genes.

Therapeutic Injections

Injections include a wide variety of therapeutic agents, e.g., for the treatment of cancer, infection, cardiovascular disease, arthritis and other inflammatory diseases, diabetes, hormonal deficiencies, central nervous system problems, and many other disease states. There are more than 400 injection products listed in the USP and, because of the huge number of biotechnology molecules in clinical study, this number will continue to grow rapidly over the next several years. Injections are primarily solutions containing the active ingredient and other substances. Product solutions are available either as "ready-to-use" (e.g., amobarbital sodium for injection) or solutions after reconstituting lyophilized (e.g., Gemzar®) or crystallized dry powder products (including many injectable cephalosporins). Some solutions may contain only the drug, e.g., vancomycin hydrochloride solution after reconstitution. Some products are suspensions in which the drug is suspended in a suitable medium, again either commercially available as a ready-to-use suspension (e.g., Humulin® N) or reconstituted as a suspension rather than as a solution (e.g., amoxicillin for injectable suspension). Injections can also be commercially available as concentrated liquids (e.g., potassium chloride for injection concentrate) that must be diluted before administration. Injectable products are either single dose or multiple dose. Multiple-dose

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injections must contain an antimicrobial preservative agent(s), and the volume of injection should not exceed 30 ml (8).

Ophthalmic Products (9)

Ophthalmic drug products include drugs in solution, suspension, gel, or ointment, administered topically to the corneal surface of the eye. Ophthalmic products also include irrigating solutions in LVI sizes. There are many different types of ophthalmic drug products to treat glaucoma, infection, inflammation, and other diseases of the eye. Ophthalmic products must be sterile, but because they are topically applied, they are not required to be pyrogen-free. Ophthalmic solutions and suspensions are usually packaged in squeezeable low-density polyethylene containers for easy administration. Ophthalmic ointments are also sterile and must be free from metallic particles; they are packaged in ointment tubes. Because ophthalmic products are multiple-dose products, they must contain antimicrobial preservative agents. Because of plastic packaging, most ophthalmic products are aseptically processed.

Diagnostic Agents Including Diagnostic Radiopharmaceuticals (10)

There are many SVI diagnostic agents available including solutions containing contrast media and solutions containing radioactive iodine, chromium, technetium, iron, and other radioactive elements. These products are used primarily to evaluate organ functions. Contrast media solutions are stable in solution and, in fact, can be terminally sterilized. Most radioactive agents are produced to be used within hours of preparation because of the very short half-lives of the radioactive element. As with other sterile dosage forms, diagnostic agent products are to be sterile, pyrogen-free, and particulate-free.

Allergenic Extracts (11)

Allergenic extracts are sterile concentrates (solutions or suspensions) of the substances (allergens) responsible for unusual sensitivities in humans. These products can be used for therapeutic or diagnostic purposes. Extracts are aqueous (0.9% sodium chloride used as the diluent) or glycerinated (50% glycerin as the diluent). Most preparations are buffered at pH 8 and contain phenol ($\leq$0.4%) as an antimicrobial preservative. They are sterilized by aseptic filtration.

FORMULATIONS

Small-volume injectables are usually considered small-volume solutions in vials or ampuls but are available in a variety of dosage forms and packaging systems.

Liquids

Small-volume injectable liquids are primarily aqueous solutions. However, because many important therapeutic agents are poorly soluble or totally insoluble in water, oily solvents and water-miscible cosolvents are used to produce ready-to-use solutions.

Aqueous solutions

Aqueous ready-to-use SVIs contain the active ingredient, additional substances, if necessary, and water as the solvent. Water-for-injection (WFI), USP, is the solvent of choice for aqueous SVIs. WFI is prepared by distillation or reverse osmosis techniques. Of all the USP types of water (Table 1), WFI is the purest form of water available for sterile products. An essential requirement of WFI is its freedom from pyrogenic contamination. WFI and other USP types of water are now required to pass a certain specification for endotoxin concentration (see Table 1). Endotoxins are pyrogens with pyrogens being metabolic byproducts of microbial growth and death that cannot be destroyed by autoclaving or by sterilizing membrane filters. Aqueous SVI solutions are prepared either by filling the product into containers, sealing, and terminally sterilizing the finished product or, for drugs that cannot physically or chemically withstand high temperatures or radiation doses required for terminal sterilization, the drug product is sterile-filtered and aseptically filled into the final container and the container sealed by aseptic processing.

Nonaqueous solutions

Several SVIs are marketed as oily solutions (Table 2). The oil must be of vegetable origin (sesame, olive, or cottonseed oils are most commonly used) because of safety, purity, and biocompatiblity considerations. Oils for injection must meet USP requirements (12):

1. Solid paraffin test (measurement of oil clarity);
2. Saponification value between 185 and 200;
3. Iodine value between 79 and 128; and
4. Test for unsaponifiable matter and free fatty acids.

Oily solutions are prepared by separately sterilizing the solvent, usually using dry heat, and the drug (dry heat or a gas such as ethylene oxide), then combining the solvent and drug aseptically. Terminal sterilization cannot be used for

Table 1 Types of water described in the *United States Pharmacopeia*

Type	Preparation	Pyrogen-Free	Comments
Purified water USP	Distillation or ion exchange	No	Pharmaceutical solvent
Water for injection USP (WFI)	Distillation or reverse osmosis	Yes[a]	Not sterile. Must be used within 24 h or stored below 5°C or ≥80°C; used for manuf. of parenteral products to be sterilized
Sterile water for injection USP	Distillation or reverse osmosis	Yes[a]	Same as WFI; single-dose containers; also used to reconstitute sterile solids and dilute sterile solutions
Bacteriostatic water for injection USP	Distillation or reverse osmosis	Yes[a]	Multiple and single dose
Sterile water for irrigation USP	Distillation or reverse osmosis	Yes[a]	1 L or larger, wide mouth, does not meet particulate matter requirements for LVI; labeled "For Irrigation Only"

[a] ≤0.25 endotoxin units per mL.

oily solutions because of the lack of moisture in the product necessary to generate saturated steam under pressure required to destroy microbial life. Practical development experiences with oily injection formulations have been reported by Sims and Worthington (13) and Radd et al. (14).

Cosolvent

A fairly large number of SVIs contain cosolvent systems; a partial listing of commercial products is given in Table 3.

Table 2 Small-volume parenteral products containing oil(s) as the solvent system

Product, USP XXII	Oil
Ampicillin (suspension)	Vegetable
Desoxycorticosterone acetate	Sesame
Diethylstilbestrol	Sesame, cottonseed
Dimercaprol (suspension)	Peanut
Epinephrine (suspension)	Sesame
Estradiol benzoate	Sesame
Estradiol cypionate	Cottonseed
Estradiol valerate	Sesame
Estrone	Sesame
Ethiodized iodine	Poppyseed
Fluphenazine enanthate	Sesame
Hydroxyprogesterone caproate	Sesame
Menadione	Sesame
Nandrolone decanoate	Sesame
Penicillin G procaine (suspension)	Vegetable
Propyliodone (suspension)	Peanut
Testosterone cypionate	Cottonseed
Testosterone enanthate	Sesame
Testosterone propionate	Sesame

(From Ref. 4.)

Cosolvents are used to increase the solubility of the poorly soluble drug in water. Cosolvents also tend to minimize or even prevent drug chemical degradation by hydrolysis, obviously because of the reduction in the percentage of water in the system. Water-miscible cosolvents operate on the principle of lowering the dielectric constant property of water, thereby increasing the aqueous solubility of poorly water-soluble drugs. Depending on drug stability, products containing cosolvents can be sterililized terminally using saturated steam under pressure. Otherwise, such products are prepared by aseptic processing. A primary concern in using cosolvents in injectable formulations is their potential to cause lysis of red blood cells when administered intravenously (15). Therefore, any addition of a cosolvent to a formulation intended for parenteral administration must be studied for its safety and potential toxicological effects.

Solids

SVIs are available as sterile dry solids that must be reconstituted with a diluent, usually sterile water for injection, USP, before being administered as a solution or suspension. Sterile dry SVIs are prepared using two primary methods.

Freeze-drying

Most commercial sterile dry powders are manufactured by freeze-drying, also called lyophilization. In this process, under strict aseptic conditions, the product is aseptically filtered and filled as a solution. Special slotted rubber closures are inserted partially onto the vials, which are then transferred to a freeze dryer. Freeze-drying involves three primary operations:

Table 3 Small-volume parenteral products containing cosolvents

Trade Name	Manufacturer	Cosolvent composition
Dramamine	Searle	50% propylene glycol
Apresoline	Ciba	10% propylene glycol
MVI	US Vitamins	30% propylene glycol
Nembutal	Abbott	40% propylene glycol, 10% ethanol
Luminal	Winthrop	67.8% propylene glycol
Dilantin	Parke-Davis	40% propylene glycol, 10% ethanol
DHE 45	Sandoz	15% glycerin, 6.1% ethanol
Cedilanid	Sandoz	15% glycerin, 9.8% ethanol
Robaxim	Robbins	50% polyethylene glycol
Serpasil	Ciba	50% polyethylene glycol, 10% dimethylamine
Ativan	Wyeth	20% polyethylene glycol, 80% propylene glycol
Librium	Roche	20% propylene glycol
Valium	Roche	40% propylene glycol, 10% ethanol
Lanoxin	Burroughs Wellcome	40% propylene glycol, 10% ethanol

From Yalkowsky, S.; Roseman, T., *Techniques of Solubilization of Drugs*; Marcel Dekker, Inc.: New York, 1981; 91.

1. Freezing the product below its eutectic temperature (for crystalline materials) or below its glass transition temperature (for amorphous materials);
2. Primary drying in which the frozen solvent is sublimed, a phase transition from a solid directly to a gas; and
3. Secondary drying in which solute bound water is removed to an acceptable product moisture level for long-term stability.

At the completion of the freeze-dry cycle, the partially inserted rubber closures are fully seated in the vials. The finished product contains a white or off-white sterile dry powder.

Freeze-drying operations are used because of limited stability of certain drugs in solution. Most therapeutic proteins are unstable in solution and can only be commercial products if they are freeze-dried. Freeze-dried formulations usually contain bulking agents (e.g., mannitol) that provide an esthetic dry solid matrix and can help in stabilizing the drug in the solid state. Other excipients are added to the freeze-dried formulation for various reasons, primarily to aid in product chemical and/or physical stabilization (e.g., buffers, antioxidants, cyroprotectants). Freeze-dried vials are usually stable for at least 2 years at ambient conditions, except for some protein products that might need to be refrigerated and have a shorter shelf life. Once the freeze-dried product is reconstituted, normal shelf-life storage conditions are 24 h at room temperature and up to 1 week under refrigeration. Excellent freeze-drying science and technology reviews are available (16, 17).

Powder-filled SVIs

Many SVI antibiotics, particularly the injectable cephalosporins, as well as other molecules are manufactured by sterile crystallization of the active ingredient and aseptically filling the sterile powder into the final container. The drug is dissolved in an appropriate solvent, then filtered through a 0.2-μm membrane filter. Several techniques can be used for sterile crystallization, including adding sterile seed crystals and adjusting the pH level or adding a sterile antisolvent in which the drug is insoluble. The resultant slurry is collected on a filter system (e.g., the Buchner funnel) and dried, then the dried crystals are milled and blended. Obviously, for this approach to work, the drug must be able to be crystallized. Several variables are critical in controlling the purity and quality of the final crystals, including temperature, rate of addition of solvent, adjustment of pH level, mixing rate and time, and the quality of the seed crystals. Sterile crystallization followed by powder-filling is much more economical than freeze-drying. However, sterile powder-filling offers greater challenges with respect to process variability, microbial and particulate contamination, and operator sensitivity.

Suspensions (18)

With sterile suspensions, the active drug ingredient is suspended in a liquid carrier before administration. Commercial suspensions are either ready to use or dry powders reconstituted as suspensions. Drugs

are formulated as suspension dosage forms for one of two reasons:

poor solubility in aqueous solution but the product does not need to be administered iv, and
the need for a long-acting depot injection.

Suspension products (Table 4) are prepared by combining sterile vehicle and sterile drug powder aseptically or by combining two sterile solutions, with the drug solution precipitating in the diluent solution.

Major concerns with the suspension dosage form are:

1. Resuspendability of the drug in the vehicle to permit homogeneous filling of the product into the container and to provide homogeneous dosing when withdrawing from the container;
2. Caking or settling of the drug, resulting in a physically unstable product; and
3. Syringeability (the ability to withdraw a homogeneous dose from the vial into a syringe) and injectability (the ability to eject the product through the needle into the patient).

Formulation ingredients include the suspending agent, a wetting agent (if the suspending agent does not also serve this purpose), a buffer, and an antimicrobial preservative for multiple-dose products.

Emulsions (19)

Emulsions are mixtures of oil- and water-based vehicles with an appropriate surface-active agent to facilitate and maintain the miscibility of the oil-in-water phase. Diprivan® (propofol, a local anesthetic agent) is a primary example of an SVI emulsion. The formulation contains soybean oil, glycerol, and egg lecithin.

BASIC CHARACTERISTICS OF SVIs

SVIs must be sterile and free from pyrogens and foreign particulate matter. These three major characteristics distinguish sterile dosage forms from any other pharmaceutical product.

Sterility (20)

Sterility is a state of absolute freedom from microbial contamination. Interestingly, the word *sterile* on the label of a sterile product has had a historic meaning that a sample of the product lot passed the compendial test for sterility (21). Today, to claim that a product is sterile involves much more than passing a sterility test. Achievement of sterility involves the combination and coordination of a wide range of activities and processes such as:

Cleaning and sanitization of all facilities and equipment

Cleaning and sterilization of equipment, packaging, and all other items to be in contact with the sterile product

Installation and certification of laminar air flow areas where sterile air is provide via high-efficiency particulate air (HEPA) filters

Environmental monitoring of the facility, equipment, water, and personnel for strict microbiological and particulate control

Appropriate gowning and training of personnel in aseptic techniques

Table 4 Small-volume parenteral suspensions

Product	Manufacturer	Suspending agent
Aristocort	Lederle	Propylene glycol 4000
Bicillin C-R	Wyeth	Lecithin, carboxymethylcellulose
Decadron-LA	Merck	Carboxymethylcellulose
Depo-medrol	Upjohn	PEG 3350 (polyethylene glycol)
Duracillin	Lilly	Procaine salt
Hydeltra-TBA	Merck	Tebutate salt
Lente insulins	Lilly, Novo	Polymorphic
NPH insulins	Lilly, Novo	Protamine
PZI insulins	Lilly, Novo	Protamine, zinc
Prolixin decanoate	Princeton	Decanoate salt

Validation of sterilization processes

Validation of the filter system

Integrity testing of the filter system before and after filtration

Integrity testing of the container-closure system to maintain sterility of the product

Conductance of the sterility test initially for all lots and at the end of the shelf-life expiration dating period for the product lot under stability testing

The end-product sterility test suffers from at least three serious limitations that minimize its dependability as a sole indicator of the sterility of a lot of product.

1. Concern that the small sample (usually 20 containers per lot) truly represents the entire lot. Probability statistics reveal that with such a small sample size, the extent of contamination must be significant (on the order of at least 1% of the lot) for the sample to fail the sterility test.
2. Concern that the culture test media used for sterility testing can support the growth of low to high levels of any microbial life possibly contaminating the product.
3. Concern that no accidental contamination was introduced during the performance of the sterility test. There is a finite probability that personnel, testing environment, and/or testing materials may introduce contamination, resulting in a false-positive sterility test result. This concern has been alleviated to a great degree by the advent and successful application of barrier isolator technology systems. Such systems remove direct human contact with the sterile product samples and provide a testing environment that is validated as truly sterile.

Freedom from Pyrogens

Pyrogens are metabolic byproducts of microbial growth. Injected in sufficient amounts in humans (in fact, in any mammal), pyrogens can react with the hypothalamus of the brain to raise the body temperature. In addition, they can cause a number of other adverse physiological effects, including death. The serious problems with sepsis are a result of high levels of endotoxins, endotoxins being a major type of pyrogen. Pyrogens are very small, water-soluble, heat-resistant lipopolysaccharides that cannot be destroyed by typical steam-sterilization cycles or removed by 0.2-μm membrane filters. Prevention rather than elimination is the key for pyrogen removal. The primary source of pyrogenic contamination in parenteral products is water. Fortunately, pyrogens are destroyed by distillation. Water used to clean containers and closures can also be a source of pyrogens. However, glass is sterilized by dry heat at temperatures hot enough (usually $>250^{\circ}C$ to destroy pyrogens). Rubber closures are steam-sterilized, which does not destroy pyrogens. Closures are depyrogenated by the cleaning and rinsing process using pyrogen-free water. Chemical raw materials used in parenteral formulations must be crystallized using pyrogen-free water or other solvents. Some raw materials, e.g., sucrose, mannitol, amino acids, etc. must now be tested by incoming quality control for the presence of endotoxins. If the parenteral product is contaminated with pyrogens, there is no practical way to remove or destroy them. Ultrafiltration (nanometer; nominal molecular-weight filters) will depyrogenate and is used in bioprocessing for separating the smallest unit of lipopolysaccharide from therapeutic proteins. However, ultrafiltration is not a practical pyrogen-removal process for commercial processing of parenteral products.

Pyrogenic contamination is detected using two tests. In the older method, rabbits are injected with product samples, and rectal temperature is measured. Compendial limits are established with respect to how much temperature increase is permitted before the product is judged to be free or contaminated with pyrogens. The newer method involves a relatively simple in vitro technique called the Limulus Amebocyte Lysate (LAL) test. It is based on the high senstivity of amebocytes of the horseshoe crab (Limulus) to the lipopolysaccharide component of endotoxins originating from Gram-negative bacteria. The LAL test is now the USP method of choice with endotoxin limits established for most SVIs (22).

Freedom from Particulate Matter

Particulate matter is viewed as unacceptable contamination in parenteral solutions. It is recognized that subvisible particulate matter will exist in certain amounts, but the USP now has limits for acceptable levels of particulate matter for SVIs (no more than 6000 particles per container ≥ 0.5 μm; no more than 600 particles per container ≥ 25 μm). The USP is the only compendium in the world that contains limits for subvisible particulates in SVIs. All worldwide compendia have subvisible particle limits (particles per milliliter) for large-volume injections. SVI solutions with

visible particulate matter should not used. Particulate matter creates problems in product quality and clinical safety. The primary sources of particulate matter are the container-closure systems and personnel.

Stability

Drugs in SVIs are generally unstable. Many drugs are so unstable that they cannot be marketed as ready-to-use solutions. Drugs with sufficient solution stability will still require certain formulation, packaging, and storage conditions to maintain stability during shelf-life storage and use. The primary pathways of drug degradation involves oxidation (reaction with molecular oxygen catalyzed by various factors including high temperature, high pH level, heavy metals, light, and peroxide contaminants) and hydrolysis (reaction with water catalyzed by high temperature and extremes in pH). For protein pharmaceuticals, aggregation of the protein, resulting in a loss of potency, can be a major degradation pathway. Drugs can also react with packaging and formulation components, resulting in physical and chemical degradation.

Oxidation involves the reaction of free radicals with molecular oxygen so the combination of functional groups that can easily form free radicals, e.g., phenolic or sulfhydryl groups, catalysts (see above), and molecular oxygen, will cause a propagation of the self-oxidation process. Many SVI products are packaged in light-protective packaging, require storage at controlled room or lower (refrigeration) temperatures, are formulated at low pH, contain antioxidants and/or metal chelating agents, and are processed in "oxygen-free" conditions where water is saturated with an inert gas, and, before to sealing the container, the product is overlayed with an inert gas to remove oxygen from the headspace of the container.

Many drugs in liquid SVIs will react with water and form hydrolytic degradation products. Hydrolysis and decomposition occur as solution pH may change and are catalyzed by resulting hydrogen and/or hydroxyl ions. Buffers play an important role in certain injectable products to achieve tight control of solution pH. Hydrolysis of solid-state injectables can occur with moisture from the headspace in the container, moisture remaining in the solid product, and/or moisture originating from or through the rubber closure. Control of residual moisture during and after processing and the use of effective container-closure systems to minimize moisture ingress are very important to protect dried powders from hydrolytic degradation.

Isotonicity

SVIs should be isotonic with blood, tears, spinal fluid, and other biological fluids into which the product is injected or instilled. This means that the injected or instilled solution contains the same "number" of solute "particles" in solution as is contained in the biological cell. Isotonicity means that the "tone" of the cell will not be disturbed, either by the ingress of water from the injected solution (if the solution is hypotonic) or egress of water from the cell (if the solution is hypertonic). Solution tonicity can be ascertained by measurement of a colligative property such as osmostic pressure or freezing-point depression. Biological cells are semipermeable membranes, meaning that they allow the passage of water (and some solutes such as boric acid) but do not allow passage of most solutes. Thus, for example, if a hypotonic solution is injected or instilled, there are fewer solute "particles" in the solution than there are in the cell, forcing water from the injected solution to pass through the cell membrane in an attempt to equalize pressure on both sides of the cell membrane. Increasing the water level of the cell may lead to the cell bursting, which, for red blood cells, is a phenomenon called hemolysis. Hypertonic solutions administered cause the opposite effect, whereby water from the cells permeate the membrane to equalize pressure, and the cells shrink (crenation). In either case, cellular damage can occur causing pain and tissue irritation or damage. Blood, muscle, and subcutaneous cells can withstand a fairly wide range of osmotic pressures from injected solutions (e.g., 250–350 mOsm/kg), whereas tear and spinal fluid cells are much more sensitive to slight differences in the osmotic pressure of injected or instilled solutions. In practice, wide osmolality ranges of SVIs can be tolerated when injected except for injections in cerebrospinal fluid (intrathecal, intraspinal, intracisternal injections). However, it is also true that for all injections, achieving isotonicity should be a goal of the product formulation scientist.

FORMULATION INGREDIENTS

SVIs are simple formulations compared with other pharmaceutical dosage forms. Solution SVIs contain water, the active ingredient, and a minimal number of inactive added ingredients. Solid SVIs contain the active ingredient and usually one or two added ingredients. Formulation scientists have severe restrictions in number and choice of added substances because of safety considerations.

Solvent

The most widely used solvent for SVIs is water for injection (WFI), USP. As a solvent, WFI is used in preparing the bulk solution (compounding) and as a final rinse for equipment and packaging preparation. WFI is prepared by distillation or reverse osmosis, although only distillation is permitted for sterile water for injection, USP. Sterile water for injection is used as a vehicle for reconstitution of sterile solid products before administration and is terminally sterilized by autoclaving. Bacteriostatic water for injection, USP, is commercially available as a reconstitution vehicle for solid products intended for multiple-dose use. Benzyl alchohol is a common antimicrobial preservative used in bacteriostatic water for injection.

Sesame oil, cottonseed oil, and other vegetable oils are used as vehicles for water-insoluble drugs such as corticosteroids and oil-soluble vitamins. Oily solutions can be administered only by intramuscular injection.

Solubilizers

Solubilizers are used to enhance and maintain the aqueous solubility of poorly water-soluble drugs (23–27). Examples of solubilizing agents used in sterile products include:

1. *Liquid cosolvents*: glycerin, polyethylene glycol (300, 400, 3350), propylene alcohol, and ethanol, Cremophor EL, sorbitol
2. *Surface active agents*: polysorbate 80 (polyoxyethylene sorbitan monooleate), polysorbate 20, Pluronic 68, lecithin
3. *Complexing agents*: β-Cyclodextrins, Captisol®, polyvinylpyrrolidone, carboxymethylcellulose sodium

Liquid solubilizers act by reducing the dielectric constant properties of the solvent system, thereby reducing the electrical conductance capabilities of the solvent and increasing the solubility of hydrophobic or nonpolar drugs. Lanoxin,® Valium,® and Nembutal® are examples of commercially available sterile solutions containing cosolvent solubilizers. A popular combination consists of 40% propylene glycol and 10% ethanol in water.

Surface active agents increase the dispersability and water solubility of poorly soluble drugs owing to their unique chemical properties of possessing both hydrophilic and hydrophobic functional groups in the same molecule (the same is true of β-Cyclodextrins, addressed below). The hydrophobic groups adsorb to surface molecules of the drug, whereas the hydrophilic groups interact with the water-solvent molecules. Therefore, the drug molecules locate within the hydrophobic core of the surface active agent (sometimes called a micelle) while the polar molecules of the surface active agent are oriented with water, and the drug is solubilized within the surface active agent dissolved in water.

Solid solubilizers such as the β-Cyclodextrins act by forming soluble inclusion complexes in aqueous solution. These molecules, as with surface active agents, are amphiphilic, meaning that they contain hydrophobic interior functional groups and hydrophilic hydroxy exterior functional groups that enable insoluble drugs to remain in the interior core and be solubilized in water. Brewster, et al. (28) reviewed the application of cyclodextrins in parenteral formulations, particularly for the solubilization and stabilization of proteins and peptides. A relatively new cyclodextrin, Captisol®, has gained prominence as a safe and effective solubilizer and stabilizer (29). It is an anionic β-Cyclodextrin with a sulfobutyl ether substituent.

Antimicrobial Preservative Agents

Antimicrobial preservatives serve to maintain the sterility of the product during its shelf life and use. They are required in preparations intended for multiple dosing from the same container because of the finite probability of accidental contamination during repeated use. They also are included, although this is quite controversial, in some single-dose products that are aseptically manufactured to provide additional assurance of product sterility. The combination of antimicrobial preservative agents and adjunctive heat treatment (usually temperatures below 110°C) also is used to increase assurance of sterility for products that cannot be terminally sterilized. Very few antimicrobial preservative agents are acceptable (Table 5), with this list decreasing as agents such as thimerosal (and other mercury-containing preservatives) and chlorobutanol are no longer being used. Most substances with antimicrobial activity are irritating and toxic at relatively low concentrations and usually have stability limitations (hydrolytic or oxidative degradation). They can be incompatible with the drug and formulation ingredients and can interact adversely with packaging components. Most commonly used parenteral antimicrobial preservatives are alcoholic or phenolic chemicals. These are highly toxic even at low concentrations and easily oxidizable, and their volatility can cause problems with rubber closure permeation. Formulation scientists must also be aware of significant differences comparing USP and EP requirements for preservative efficacy. Basically, the USP

Table 5 Antimicrobial preservative agents in Small-volume parenterals

Agent	Concentration range (%)	Products
Phenol	0.065–0.5	Humulin N, Zantac, Tensilon, Tagamet, Phenergan, Imferon
m-Cresol	0.16–0.3	Humulin N, Humulin R, Humatrope, Demerol
Methylparaben	0.05–0.18	Decadron, Elavil, Prostigmin
Propylparaben	0.011–0.035	Garamycin, Prolixin, Bicillin
Chlorobutanol	0.5–0.55	Epitrate, Bentyl, Dopram
Benzyl alcohol	0.75–2.0	Valium, Protropin, Geopen, Compazine, Pronestyl, Cleocin
Benzalkonium chloride	0.01–0.025	Most ophthalmic products
Thimerosal	0.0075–0.01	Neosporin, Rhogam, Wydase

requires a bacteriostatic preservative system, whereas the EP requires a bacteriocidal preservative system. For example, whereas the USP requires a 1-log reduction 7 days after a bacterial challenge population is added to the product containing the antimicrobial preservative, the EP Criteria A requirement is a 3-log reduction in bacterial population after 1 day.

Buffers

Buffers are used to maintain the pH level of a solution in the range that provides either maximum stability of the drug against hydrolytic degradation or maximum or optimal solubility of the drug in solution. The most common buffer systems used in SVIs are listed in Table 6. Buffers are composed of simple weak acids and their corresponding salt forms. The appropriate choice of buffer depends on the pH range in which the drug in question is most stable (or most soluble) that matches the pK_a (dissociation constant) of the buffer species. For example, if a pH of 4.5 is most desirable, the correct choice of buffer would be an acetate buffer because the pK_a of acetic acid is 4.76. At pH 4.76, acetic acid exists 50% as the acid (un-ionized form) and 50% as the salt (ionized form). Sufficient acid and salt species exist at this pH level to compensate for any potential drifts in solution pH and maintain the desired pH level. The concentration of buffer depends on strength of buffer capacity required to maintain the pH level within the desired range. Obviously, the higher the concentration, the greater the buffer capacity. However, high buffer concentrations can lead to other problems such as general acid/base catalysis of drug hydrolytic reactions.

Table 6 Common buffer systems used in small-volume parenteral products

pH	Buffer system	Concentration (%)
3.5–5.7	Acetic acid–acetate	1–2
2.5–6.0	Citric acid–citrate	1–5
6.0–8.2	Phosphoric acid–phosphate	0.8–2
8.2–10.2	Glutamic acid–glutamate	1–2

Antioxidants (30)

Antioxidants function by reacting preferentially with molecular oxygen and minimizing or terminating the free radical auto-oxidation reaction. Many drugs are sensitive to the presence of oxygen and will degrade very rapidly in the absence of protection. In addition to the use of antioxidants, other precautions must be taken. These include protection from light, heat, heavy metal and peroxide contamination, and excessive exposure to air. Formulating the product at low pH is preferable if the product is stable and soluble at low pH. Common antioxidants are shown in Table 7. The most widely used agent is sodium bisulfite because its oxidation-reduction potential lies in the range at which it does not preferentially oxidize too slowly or too rapidly. Other sulfurous acid salts also are effective antioxidants, as are ascorbic acid and sodium ascorbate. Sometimes, combinations of antioxidants strengthen oxidative drug protection as well as the combination of an antioxidant and a chelating agent. The most common chelating agent used in parenterals is disodium ethylenediaminetetraacetic acid (DSEDTA).

Protein Stabilizers

Therapeutic proteins and peptides have exploded on the pharmaceutical scene in recent years. There are at least 30 commercial protein products currently marketed and hundreds more in clinical study. Proteins are very reactive

Table 7 Antioxidants commonly used in small-volume parenterals

Antioxidant	Concentration range (%)
Water soluble	
Sulfurous acid salts	
Sodium bisulfite	0.05–1.0
Sodium sulfite	0.01–0.2
Sodium metabisulfite	0.025–0.1
Sodium thiosulfate	0.1–0.5
Sodium formaldehyde sulfoxylate	0.005–0.15
Ascorbic acid isomers	
L- and D-Ascorbic acid	0.02–1.0
Thiol derivatives	
Acetylcysteine	0.1–0.5
Cysteine	0.1–0.5
Thioglycerol	0.1–0.5
Thioglycolic acid	
Thiolactic acid	
Thiourea	0.001–0.05
Dithiothreitol	
Glutathione	
Oil soluble	
Propyl gallate	0.05–0.1
Butylated hydroxyanisole	0.005–0.02
Butylated hydroxytoluene	0.005–0.02
Ascorbyl palmitate	0.01–0.02
Nordihydroguaiaretic acid	0.01–0.05
α-Tocopherol 9	0.05–0.075

with their environment, with such reactions causing protein degradation. In pharmaceutical dosage forms, proteins are potentially quite reactive with water, formulation components, packaging components, and air. Environmental conditions that promote protein degradation include high temperature, pH excursions, light, oxygen, moisture, and mechanical stress. Degradation reactions are both chemical and physical, with physical stabilization often more challenging than chemical stabilization. Proteins easily aggregate under a variety of conditions, particularly at temperature extremes and with excessive mechanical manipulations. Denaturation in the form of aggregation can occur during the freezing and/or drying and subsequent storage of proteins processed by lyophilization. A number of ingredients have been shown to stabilize proteins both in the solution state and in the dry state (31–34). Serum albumin will compete with therapeutic proteins for binding sites in glass and other surfaces and minimizes loss of the protein caused by surface binding. With concern about viral contamination in natural substances like albumin, other competitive binding agents are being investigated (e.g., hetastarch). A number of different types of substances are used as cryoprotectants and lyoprotectants to minimize protein denaturation during freeze-drying. Primary examples include amino acids (glycine, lysine, glutamine); polyhydric alcohols (sorbitol, glycerol, polyethylene glycol); nonreducing sugars (sucrose, trehalose); and polymers such as polyvinylpyrolidone, methylcellulose, and dextran. Surface active agents, such as polysorbate 80, polysorbate 20, and poloxamer 188 (Pluronic 68), are widely used to minimize protein aggregation at air/water and water/solid interfaces. Buffers, antioxidants, and chelating agents also are used to stabilize proteins in solution when necessary.

Tonicity Adjusters

A variety of agents are used in sterile products to adjust tonicity. Most common are simple electrolytes such as sodium chloride or other sodium salts and nonelectrolytes such as glycerin and lactose. Tonicity adjusters are usually the last ingredient added to the formulation after other ingredients in the formulation are established and the osmolality of the formulation measured. If the formulation is still hypotonic (i.e., $<$280 mOsm/kg as measured by a commonly used osmometer instrument), tonicity adjusting agents are added until the formulation is isotonic. If the formulation is hypertonic, the degree of hypertonicity and the intended route of drug administration need to be considered. For intravenous administration, hypertonicity values up to approximately 360 mOsm/kg are not considered harmful. However, for other routes of administration, efforts should be made to make the final product isotonic before administration. This can be accomplished either by reducing concentrations of ingredients, if acceptable, or by diluting the product before administration.

Other Ingredients

Bulking agents are used in freeze-dried preparations to increase the solid content of the "plug" in the container after the sublimation process during the freeze-drying cycle. Bulking agents not only serve to enhance the elegance of the product but also can serve as stabilizers in adsorbing excess moisture during shelf life. Suspending agents keep the drug suspended in the solvent after shaking and allow homogeneous dosing of the suspended drug from the container. Emulsifying agents lower the interfacial tension of an oil and water interface to allow the two immiscible solvents to mix and form a stable emulsion

dosage form. Semisolid agents aid in the dispersibility of the drug in ophthalmic ointments and provide the ointment base. Examples of these different additives are:

1. *Bulking agents*: mannitol, lactose, sucrose, dextran
2. *Suspending agents*: carboxymethylcellulose, methylcellulose, gelatin, sorbitol
3. *Emulsifying agents*: lecithin, polysorbate 80
4. *Ophthalmic ointment bases*: petrolatum

Two comprehensive references are available that list type and concentration of all excipients used in commercial sterile formulations that should be part of every sterile formulation scientist's library (34, 35).

PACKAGING

The packaging system obviously is an integral part of the parenteral product, providing long-term protection and maintenance of physical and chemical stability of the product formulation. Packaging can also be used as a drug delivery tool by providing more convenient delivery of the drug product (e.g., syringes, dual chamber vials) and offering better control of drug dosing (e.g., cartridges). Packaging is a major source of particulate contamination and can contribute to physical and chemical degradation of the product. Packaging constituents can leach into the product or the product can be adsorbed or absorbed. The primary types of packaging systems are glass, rubber, and plastic. Metal tubes for ophthalmic ointments are not addressed here. Primary SVI packaging systems include glass sealed ampuls, rubber closed vials, prefilled syringes, cartridges, and small- and large-volume bottles made either of glass or plastic.

Glass (36)

Glass used for parenteral products is classified as type I, type II, and type III (Table 8). Type I is the highest quality grade, composed almost exclusively of borosilicate (silicon dioxide), making it chemically resistant to extreme acidic and alkaline conditions. Type I glass, although more expensive, is preferred for most parenteral products. Often, even type I glass must be surface treated with agents such as ammonium sulfate or silica dioxide to remove surface leachates. Type II glass is made of soda-lime glass but is treated with sodium sulfite or sulfide to neutralize surface alkaline oxides. Type III glass is untreated soda-lime glass. Type II glass generally is used for large-volume injectables and for small-volume products if the solution pH level is less than 7.0. Type III glass can only be used for oily solutions and dry powders. The USP (37) and other compendia provide requirements and tests necessary to qualify the different types of glass.

Formulation scientists must be aware that glass can and will leach out various elements such as boron, sodium, potassium, calcium, iron, and magnesium. Glass leachates can affect solution pH and cause precipitation problems if the drug or other formulation component forms insoluble salts when combined with these leachates. Solutions of high pH level are notorious for causing alkali leachates. Quality control of each lot of glass must be consistent to control these potential difficulties with leachates. Glass particulates can also be a problem owing to delamination of the inner surface of the glass.

Amber glass containers can be used for light-sensitive SVIs. The amber color is produced by the addition of iron and manganese oxides to the glass formulation. Oxide leachates can occur and catalyze oxidation reactions.

Rubber (38)

Rubber formulations are used as rubber closures (vials, cartridges); rubber plungers (syringes, cartridges); and other applications (rubber septum in dual chamber

Table 8 Glass used for small-volume parenterals

Type	General description	USP test	Size (ml)	Limits (ml of 0.02 *N* acid)
I	Highly resistant, borosilicate glass	Powdered glass	All	1.0
II	Treated soda-lime glass	Water attact	100 or less	0.07
			Over 100	0.2
III	Soda-lime glass	Powdered glass	All	8.5
NP[a]	General-purpose soda-lime glass	Powdered glass	All	15.0

[a]For nonparenteral articles.

Table 9 Autoclavable rubber compounds used in small-volume parenterals

Type	Additives	Water–vapor permeation	Potential reactivity with product
Butyl	Moderate	Low	Moderate
Natural	High	Moderate	High
Neoprene	High	Moderate	High
Polyisoprene	High	Moderate	Moderate
Silicone	Moderate	Very high	Low

vials, rubber septum for needle introduction in administration set tubing). The formulations can be very complex. Not only do they contain the basic rubber polymer, but also they may contain many additives such as plasticizers, fillers, vulcanizing agents, pigments, activators, accelerants, and antioxidants. Many of these additives are not fully characterized for content or purity and can be sources of physical and chemical degradation problems in parenteral products. The formulation scientist must work as closely with the rubber manufacturer as with the glass manufacturer to choose the appropriate rubber formulation having consistent specifications and characteristics to maintain product stability.

The most common rubber polymers used in SVI closures are natural and butyl rubber (Table 9). Silicone and neoprene also are used but less frequently in sterile products. Butyl rubber has great advantages over natural rubber in that butyl rubber requires fewer additives, has low water vapor permeation properties, and has good characteristics with respect to gaseous (e.g., oxygen) permeation and reactivity with the active ingredient.

Problems with rubber materials include leaching of constituents (e.g., zinc) into the product, adsorption of active ingredients or antimicrobial preservatives, and coring of the rubber by repeated insertion of a needle. Coring produces rubber particulates that affect the quality and, potentially, the safety of the product.

Siliconization of rubber closure is a common practice in manufacturing to facilitate movement of the closure through stainless steel equipment on the filling lines. However, silicone is incompatible with hydrophobic drugs. Excessive silicone on rubber can potentiate protein aggregation and cause precipitation problems with certain drugs. Elastomer manufacturers have developed rubber formulations with specially bonded coatings that provide "slippery" rubber surfaces and, thus, do not require the need to apply silicone for high-speed processing equipment.

Plastic

Plastic packaging has always been important for ophthalmic drug dosage forms and is gaining in popularity for injectable dosage forms. Plastic bottles are used to enable people to apply droplets of medication into the eye. Plastic bottles for LVIs have been used for many years. Plastic vials for SVIs may be a wave of the future. Plastic packaging offers such advantages of cost savings, elimination of the problems caused by breakage of glass, and increase convenience of use. As with other packaging systems, plastic formulations can interact with the product, causing physical and chemical stability problems. Plastic formulations are less complicated than are rubber formulations and tend to have a lower potential for leachability of its constituents. However, plasticizer leachates are well-known with polymers such as polyvinyl chloride containers used for LVI bags and administration devices. The most commonly used plastic polymer for ophthalmic products is low-density polyethylene. For other SVIs, polyolefin formulations are widely used as well as polyvinyl chloride, polypropylene, polyamide (nylon), polycarbonate, and copolymers such as ethylene vinyl acetate.

STORAGE

Proper storage of SVIs is critical for the safety and potency of the active ingredient(s) contained in the packaging system. Long-term stability studies are necessary for the appropriate storage conditions. Stability studies involve storing the product at various temperatures, exposing to light, exposing to various relative humidities, and assessing the effect of mechanical stress

during transportation and handling. Studies on proper storage conditions and appropriate handling are extremely important in this age of global distribution of drug products, particularly products containing temperature- and stress-sensitive biomolecules. In addition to concerns regarding the maintenance of chemical and physical stability of the drug product during distribution and storage, there is also concern that the container-closure system is adequate to maintain sterility and other microbiological quality attributes of the sterile product. Container-closure integrity studies in recent years have taken on greater prominence as regulatory groups such as the FDA require these data in registration approvals and in the routine conducting of stability studies. Excellent references on container-closure integrity methods are available (39, 40).

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